Method to estimate the approximate samples size that yield a certain number of significant GWAS signals in polygenic traits

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Abstract

To argue for increased sample collection for disorders without significant findings, researchers resorted to plotting, for multiple traits, the number of significant findings as a function of the sample size. However, for polygenic traits, the prevalence of the disorder confounds the relationship between the number of significant findings and the sample size. To adjust the number of significant findings for prevalence, we develop a method that uses the expected noncentrality of the contrast between liabilities of cases and controls. We empirically find that, when compared to the sample size, this measure is a better predictor of number of significant findings. Even more, we show that the sample size effect on the number of signals is explained by the noncentrality measure. Finally, we provide an R script to estimate the required sample size (non-centrality) needed to yield a pre-specified number of significant findings.

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To illustrate the tractability of complex diseases, researchers intuitively plot/regress^{1,2} the number of significant findings, n_s , by the sample size, N , (see Fig.2 in Kim et al¹ and Fig. 3 in this paper). Early in the GWAS era such a plot suggested that the number of significant hits is approximately linear after the emergence of the first genome wide significant finding (Mark Daly PGC presentation). While such analyses are definitely informative, for polygenic traits such plots are confounded by the trait prevalences (Fig. 2 in Gratten et al³). For a better characterization of trait effect size that is not cryptically influenced by prevalence, we propose an approach to adjust traits for their prevalences and provide an empirical relation between such normalized variables and the number of significant findings for given sample sizes.

Let us assume the existence of biologically informative covariates, e.g. gender and ancestry principal components, which helps us in recovering the liability to disease (even up to a multiplication factor), L , for both cases and controls for a binary trait (BT) of prevalence K . (It should be noted that working on the liability scale, instead of the natural binary case control scale, is also supported by the Invariance Principle of statistical mathematics⁴, which states that the inference should not be affected by the scale/transformations one chooses to employ.) For the threshold-liability model, let the threshold be $\tau_K = \Phi^{-1}(1 - K)$, where Φ^{-1} is the inverse cumulative distribution function of the Gaussian distribution. In a threshold-liability model $L \geq \tau_K$ for cases and $L < \tau_K$ for controls. Thus, for a study consisting of N_1 cases and N_2 controls, the normalized effect size (δ), i.e. the difference in liability between cases and controls after adjusting for its standard error, is:

$$\delta(N_1, N_2) = \frac{E(L|L \geq \tau_K) - E(L|L < \tau_K)}{\sqrt{\frac{\text{Var}(L|L \geq \tau_K)}{N_1} + \frac{\text{Var}(L|L < \tau_K)}{N_2}}} \quad (1).$$

If φ is the probability density function for the Gaussian distribution, after substituting the expressions for expectation and variance of truncated Gaussian distributions⁵, relationship (1) becomes:

$$\delta(N_1, N_2) = \frac{\frac{\varphi(\tau_K)}{1-\Phi(\tau_K)} - \frac{-\varphi(\tau_K)}{\Phi(\tau_K)}}{\sqrt{\frac{1+\tau_K \frac{\varphi(\tau_K)}{1-\Phi(\tau_K)} - \left(\frac{\varphi(\tau_K)}{1-\Phi(\tau_K)}\right)^2}{N_1} + \frac{1-\tau_K \frac{\varphi(\tau_K)}{\Phi(\tau_K)} - \left(\frac{\varphi(\tau_K)}{\Phi(\tau_K)}\right)^2}{N_2}}} = \frac{\frac{\varphi(\tau_K)}{K} + \frac{\varphi(\tau_K)}{1-K}}{\sqrt{\frac{1+\tau_K \frac{\varphi(\tau_K)}{K} - \left(\frac{\varphi(\tau_K)}{K}\right)^2}{N_1} + \frac{1-\tau_K \frac{\varphi(\tau_K)}{1-K} - \left(\frac{\varphi(\tau_K)}{1-K}\right)^2}{N_2}}} \quad (2).$$

However, most often researchers work with the χ^2 distribution and, on this scale, the non-centrality parameter of contrasting case and control liabilities is $\lambda(N_1, N_2) = \delta^2(N_1, N_2)$. In turn, detection power is increasing with increased non-centrality parameter.

While equation (2) is derived for binary traits, it can be extended to quantitative traits (QT). For instance, we can use a first order approximation for QT as a case control trait with prevalence of 50% (i.e. a contrast above median height vs. below median height). While, in practice, such a discretization approach leads to power loss, we stress that the GWAS statistics are already obtained using a QT. The above/below median approximation is only used to extend the use of equation (2). With this preparatory work, the noncentrality per case and control unit ($N_1 = N_2 = 1$), $\lambda(1,1)$, increases by ~60% with a decrease in prevalence (Fig. 1).

To empirically investigate whether λ is a better measure than N_1 , or $N = N_1 + N_2$, to describe observed n_s , we analyze the number of significant findings (Table 1) for multiple studies for some of the most widely investigated traits. Three phenotypes are chosen from each of the four investigated trait classes (see Table 1 for references): anthropometric (all QTs) and psychiatric, neurodegenerative and immune diseases (all BT). Anthropometric traits (denoted as Anthro in plot legends) are height (H), body mass index (BMI) and waist-to-hip ratio (WHR). Psychiatric (Psych) traits are the main psychiatric disorders: schizophrenia (SCZ), bipolar disorder (BD) and major depressive disorder (MDD). As neurodegenerative (Neuro) we chose Alzheimer's disease (ALZ), Parkinson's disease (PD) and multiple sclerosis (MS). Finally, we chose as immune (Immune) disorders: Crohn's disease (CD), rheumatoid arthritis (RA) and type 2 diabetes (T2D).

To assist in predicting n_s as a function of λ , we also need to determine what transformation should we use for n_s and λ/N_1 to make the relationship between n_s and λ stronger. As mentioned in the introduction, the intuitive idea is to use the identity scale, i.e. no transformation. However, given that n_s can be viewed as a sum of Bernoulli variables (0- non-significant and 1 significant), Chernoff inequality⁴ suggests that a log transformation of n_s is likely much more desirable. For effect sizes λ (and likely, as its transformation, N), the plotting of the log probability of a significant signal ($\alpha = 5 \times 10^{-8}$) as a function of noncentrality, λ , and its log transformation, also show a much better fit (Fig. 2) for the log transformation (R^2 of 99.4% vs 91%). Given that the probability of a significant find is proportional to the number of significant findings, this suggests that the log transformation is also suitable for λ .

Thus to establish the relationship between regressing $\log[n_s]$ and $\log(\lambda)$ (also $\log N_1$, $\log N$) we use a gls model (in nlme R package) assuming an autoregressive of order 1 (AR1) correlation structure for observations within the same trait (due to earlier studies being included in all subsequent meta-analysis of this disease). We used the model to test whether the effects of N and N_1 on n_s are mediated only via $\log(\lambda)$, i.e. we regressed $\log[n_s]$ on $\log(\lambda)$, $\log[N]$, $\log(N_1)$, N and N_1 . In this model, only $\log(\lambda)$ was significant (p-value of 0.025) and all the others were not (p-values of 0.58 and 0.73). Even more, stepwise elimination on non-significant variables left only $\log(\lambda)$ as significant with $\log[N]$ being the last to be eliminated with a p-values of 0.65. This result strongly suggests that the effect of N and N_1 on n_s is wholly mediated by λ and thus non-centrality is a better predictor than sample size. The gls model was also used to vividly illustrate the better performance of our theoretically chosen transformations: when using the natural sample size scale for both n_s and λ (Fig. 3), the fit ($R^2=0.42$) is much poorer than using log scale for both (Fig. 4) ($R^2=0.71$). (The similar in spirit square root transformation of λ performed only moderately worse than log.)

We stress again that the above results suggest that our proposed measure on log scale better predicts the (log) number of significant findings for traits of various prevalences. Thus, λ from relationship (1) is a desirable effect size measure that is not confounded by prevalence. Based on the gls regression of $\log[n_s]$ on $\log(\lambda)$, the best prediction for the number of significant findings is:

$$n_s = 5.6 \times 10^{-4} \lambda^{0.89} = 5.6 \times 10^{-4} \left[\frac{\left(\frac{\varphi(\tau_K)}{K} + \frac{\varphi(\tau_K)}{1-K} \right)^2}{\frac{1+\tau_K}{N_1} \frac{\varphi(\tau_K)}{K} \left(\frac{\varphi(\tau_K)}{K} \right)^2 + \frac{1-\tau_K}{N_2} \frac{\varphi(\tau_K)}{1-K} \left(\frac{\varphi(\tau_K)}{1-K} \right)^2} \right]^{0.89} \quad (3).$$

However, most of the time the researchers want to estimate the number of cases, N_1 , needed to obtain a certain number of significant findings, n_s . To this end let $N_2 = q N_1$, where generally $q > 1$ is largely known. Then equality (3) can be solved for N_1 , as follows:

$$N_1 = \left(\frac{n_s}{5.6 \times 10^{-4}} \right)^{1.124} \frac{\left[1 + \tau_K \frac{\varphi(\tau_K)}{K} - \left(\frac{\varphi(\tau_K)}{K} \right)^2 + \frac{1 - \tau_K \frac{\varphi(\tau_K)}{1-K} - \left(\frac{\varphi(\tau_K)}{1-K} \right)^2}{q} \right]}{\left(\frac{\varphi(\tau_K)}{K} + \frac{\varphi(\tau_K)}{1-K} \right)^2},$$

$$\text{or } N_1 = 4,519 n_s^{1.124} \frac{\left[1 + \tau_K \frac{\varphi(\tau_K)}{K} - \left(\frac{\varphi(\tau_K)}{K} \right)^2 + \frac{1 - \tau_K \frac{\varphi(\tau_K)}{1-K} - \left(\frac{\varphi(\tau_K)}{1-K} \right)^2}{q} \right]}{\left(\frac{\varphi(\tau_K)}{K} + \frac{\varphi(\tau_K)}{1-K} \right)^2} \quad (4).$$

To assist applied researchers in sizing their studies, we present in the Appendix the R implementation of equalities (3) and (4).

Appendix

R function for estimating the noncentrality and # cases

K- prevalence, Nca - # cases ; Nco - # controls

```
get.nonc<-function(K=K, Nca=Nca, Nco=Nco){
  tau.K<-qnorm(K, low=F)
  ncp<-(dnorm(tau.K)*(1/K+1/(1-K)))^2/((1+tau.K*dnorm(tau.K)/K-
(dnorm(tau.K)/K)^2)/Nca+(1-tau.K*dnorm(tau.K)/(1-K)-(dnorm(tau.K)/(1-K))^2)/Nco)
  ncp
}
```

R function for estimating the required # cases yielding # of signals using our formula (4)

K- prevalence, ns - # desired significant findings & q=ratio of controls to cases (often q>1)

```
get.n.cases<-function(K=K, ns=1, q=1){
  tau.K<-qnorm(K, low=F)
  N1<-4519*ns^1.124*((1+tau.K*dnorm(tau.K)/K-(dnorm(tau.K)/K)^2)+(1-
tau.K*dnorm(tau.K)/(1-K)-(dnorm(tau.K)/(1-K))^2)/q)/(dnorm(tau.K)*(1/K+1/(1-K)))^2
  N1
}
```

Figure 1. Noncentrality parameter for various traits

Figure 2. The probability of a significant signal (log scale) as a function of noncentrality on log scale (above) and identity scale (below).

Figure 3. Number of significant findings vs. sample size (without type 2 diabetes-T2D).

Figure 4. Number of significant findings vs noncentrality parameter (without T2D). Both axes are log scale.

Table 1. Table of Studies

Trait	Abbrev.	K	N cases	N controls	Ns	First author and reference
			6,800	6,800	20	Weedon ⁶
Height	H	0.5	90,000	90,000	180	Lango ⁷
			125,000	125,000	423	Wood ⁸
			2,500	2,500	1	Scuteri ⁹
			16,000	16,000	8	Willer ¹⁰
Body Mass Index	BMI	0.5	16,500	16,500	11	Thorleifsson ¹¹
			125,000	125,000	32	Speliotes ¹²
			170,000	170,000	97	Locke ¹³
			20,000	20,000	1	Lindgren ¹⁴
Waist to Hip Ratio	WHR	0.5	40,000	40,000	14	Heid ¹⁵
			110,000	110,000	49	Shungin ¹⁶
			17,500	33,500	7	PGC1 ¹⁷
Schizophrenia	SCZ	0.01 ¹⁸	20,000	37,000	22	PGC1.5 ¹⁹
			37,000	113,000	108	PGC2 ²⁰
			2,000	3,000	1	WTCCC ²¹
Bipolar Disorder	BD	0.02 ²²	7,500	9,250	2	PGC1 ²³
			10,000	15,000	5	Muhleisen (personal communication)
Major Depressive Disorder	MDD	0.15 ²⁴	9,000	9,500	0	PGC MDD ²⁵
(Recurrent MDD)		(0.05) ²⁶	6,000	6,000	2	CONVERGE ²⁶
			131,000	330,000	45	PGC2 MDD (online presentation)
			8,300	7,300	3	Naj ²⁷
Alzheimer's Disease	ALZ	0.13 ²⁷	17,000	37,000	15	Lambert ²⁸
			25,000	48,000	20	Lambert ²⁸
			1,700	4,000	2	Simon-Sanchez ²⁹
Parkinson's Disease	PD	0.02 ³⁰	3,500	30,000	8	Do ³¹
			13,700	95,000	26	Nalls ³⁰
			1,000	900	1	Baranzini ³²
Multiple Sclerosis	MS	0.002 ³²	4,800	9,300	6	De Jager ³³
			9,800	17,400	23	IMSGC ³⁴
			1,000	2,345	12	McGovern ³⁵
Crohn's Disease	CD ³⁵	0.002	3,250	4,800	33	Barrett ³⁶
			6,350	15,050	71	Franke ³⁷
			2,100	2,500	4	Jiang ³⁸
Rheumatoid Arthritis	RA	0.01 ³⁸	5,500	20,200	10	Stahl ³⁹
			20,000	620,000	57	Okada ⁴⁰
			661	614	5	Sladek ⁴¹
Type 2 Diabetes	T2D	0.1 ⁴¹	1,464	1,467	5	Diabetes at BROAD ⁴²
			5,500	14,500	20	Kooner ⁴³
			26,500	84,000	26	DIAGRAM ⁴⁴

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